Reaction of Nitrilimines with 2-Aminopicoline, 3-Amino-1,2,4-Triazole, 5-Aminotetrazole and 2-Aminopyrimidine

Rami Y. Morjan¹, Basam S. Qeshta¹, Hussein T. Al-Shayyah¹, John M. Gardiner², Basam A. Abu-Thaher¹, Adel M. Awadallah*¹

¹Department of Chemistry, Islamic University of Gaza, Gaza, Palestine
²Manchester Institute of Biotechnology, School of Chemistry and EPS, The University of Manchester, Manchester, UK
Email: awada@iugaza.edu.ps

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Abstract

The reaction of picoline derivatives 3-6 with hydrazonoylhalide 1a produced imidazo[1,2-a]pyridines 7-10, while the reaction of the same picoline derivatives with hydrazonoylhalide 1b afforded imidazo[1,2-a]pyridine-2-ones 11-13. The reaction of 1b, c with 3-amino-1,2,4-triazole 14 produced the acyclic adducts 18 and 19, respectively. Reaction of 1b, 1c with 5-aminotetrazole 20 produced the acyclic products 23 and 24, respectively. Finally, the reaction of 1b with 4, 6-dimethyl-2-aminopyrimidine 27 afforded compound 29 rather than its isomeric structure 28. The structure of the products was confirmed by the different spectroscopic analytical methods including IR, MS, ¹HNMR and ¹³CNMR.

Keywords

Nitrilimines, Picolines, Imidazo[1,2-a]Pyridine, Triazoles, Tetrazoles, Pyrimidines

1. Introduction

Nitrilimines—generally generated in situ from hydrazonoyl halides are 1,3-dipolar species that are widely used for the synthesis of different heterocyclic systems via 1,3-dipolar cycloaddition reactions [1] [2], or cyclocondensation reactions [2]. Nitrilimines with C-acetyl or ester moiety represent a dielectrophilic system that may react with dinucleophilic heterocyclic systems at the carbonyl carbon of the acetyl or ester group, and at the terminal carbon of the dipole leading to fused heterocyclic systems. Recent examples include; the synthesis of im-
dine and imidazo[1,2-a]pyrazine from the reaction with 2-aminopyrazine [5]. Their reaction with 2-cyanome-
thylen-benzimidazole gave pyrrolo[1,2-a]benzimidazole [6] [7]. The reaction of ethyl pyridine-2-acetate with
nitrilimines having a C-acetyl moiety afforded the corresponding pyrrolo[1,2-a]pyrazine, while their reaction
with nitrilimines having a C-ester moiety afforded a cyclic adducts [8]. Similarly, the reaction of nitrilimines
with a C-ester moiety with 2-cyanomethylbenzimidazole, and 2-amminobenzimidazole afforded a cyclic add-
ducts [8]. In this work, we will investigate the reaction of nitrilimines with different amino heterocycles ho p-
with a C -ester moiety with 2 -cyanomethylbenzimidazole, and 2-amniobenzimidazole afforded a cyclic ad-
ducts [8]. In this work, we will investigate the reaction of nitrilimines with different amino heterocycles hop-
ing to prepare new fused heterocyclic compounds that may be further tested for their biological activity. The
following amino heterocycles will be used; aminopicolines, aminotriazole, aminotetrazole, aminoisoxazole

2. Materials and Methods

2.1. Experimental

1H-NMR spectra were recorded at 300 or 400 MHz and 13C-NMR spectra at 75 or 100 MHz on a Bruker AC300
or AC400 spectrometer. Chemical shifts are denoted in (ppm) relative to the internal solvent standard, TMS.
ES-MS and HRMS were recorded on a Micromass LCT orthogonal acceleration time-of-flight mass spectromet-
er (positive and negative ion mode) with flow injection via a Waters 2790 separation module autosampler.
FTIR spectra were recorded using Shimadzu 8201 spectrophotometer with KBr technique in region 4000 - 400

2.1.1. General Procedure for Syntheses of Compounds 7-10 and 11-13

Triethylamine (0.6 g, 0.006 mol) in dry THF (10 ml) was dropwise added to a stirred solution of hydrazonoyl
halides and the crude products were then recrystallized from the appropriate solvents to give the title compounds.

1) 3-[(4-Chlorophenyl)diazenyl]-2,8-dimethylimidazo[1,2-a]pyridine 7

Yield 93%, Yellow solid, mp 152˚C - 155˚C; IR (KBr): V max cm⁻¹ = 1490, 1416, 1298, 1282, 1221, 1200, 1096, 811 and 774 cm⁻¹. MS: m/z C15H13ClN4 (284/286 M+), chlorine isotope effect), HRMS (Calculated 284.0902, Found 284.0898). 1H NMR (300 MHz, DMSO-d6): δ 9.62 (d, J = 7.0 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 7.0 Hz, 1H), 7.20 (t, J = 7.0 Hz, 1H), 2.74 (s, 3H, CH3), 2.58 (s, 3H, CH3). 13C NMR (100 MHz, DMSO-d6): δ 166.2, 151.4, 138.2, 136.1, 135.4, 131.2, 129.0, 127.3, 124.0, 123.0, 119.2, 15.2, 10.3

2) 3-[(4-Chlorophenyl)diazenyl]-2,7-dimethylimidazo[1,2-a]pyridine 8

Yield 78%, Yellow solid, mp 174˚C - 177˚C; IR (KBr): V max cm⁻¹ = 2993, 1520, 1473, 1462 and 796 cm⁻¹; MS: m/z C15H13ClN4 (284/286 M+), chlorine isotope effect); HRMS (284.0902, Found 284.0901). 1H NMR (300 MHz, DMSO-d6): δ 9.66 (d, J = 6.9 Hz, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H + 1H pyr.), 7.16 (d, J = 7.0 Hz, 1H), 2.71 (s, 3H, CH3), 2.49 (s, 3H, CH3); 13C NMR (100 MHz, DMSO-d6): δ 151, 149, 139, 136, 131, 129, 124, 121, 119, 111, 21, 10.

3) 3-[(4-Chlorophenyl)diazenyl]-2,6-dimethylimidazo[1,2-a]pyridine 9

Yield 94%, green solid, mp. 145˚C - 177˚C; MS: m/z C15H13ClN4 (284/286 M+), chlorine isotope effect); HRMS (284.0902, Found 284.0897). 1H NMR (300 MHz, DMSO-d6): δ 9.55 (s, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 9.0 Hz, 1H), 2.70 (s, 3H, CH3), 2.43 (s, 3H, CH3). 13C NMR (100 MHz, DMSO-d6): δ 161.0, 151.0, 138.0, 136.0, 131.0, 130.0, 129.0, 126.0, 124.0, 119.0, 111.0, 17.0, 10.0.

4) 3-[4-Chlorophenyl)diazenyl]-2,5-dimethylimidazo[1,2-a]pyridine 10

Yield 93%, orange solid, mp 157˚C - 159˚C; MS: m/z C15H13ClN4 (284/286 M+), chlorine isotope effect); HRMS (284.0902, Found 284.0908). 1H NMR (300 MHz, DMSO-d6): δ 7.74 (d, J = 9.1 Hz, 2H), 7.60 (d, J = 9.1 Hz, 2H), 7.45 - 7.60 (m, 2H, overlapped), 7.12 (d, J = 6.8 Hz, 1H), 3.00 (s, 3H, CH3), 2.71 (s, 3H, CH3).
2.25 (s, 3H, CH₃).

CH₃). 13C NMR (100 MHz, DMSO-d₆): δ 123.1 (C, aromatic ring), 117.8 (CH, aromatic ring), 24.7 (CH₃), 20.8 (CH₃), 17.1 (CH₃). 15N NMR (100 MHz, DMSO-d₆): δ 202.0, 150.0, 149.0, 140.0, 136.0, 133.0, 131.0, 130.0, 127.0, 112.0, 111.0, 18.0.

6) 6-Methylimidazo[1,2-a]pyridine-2,3-dione-3-[4-chlorophenyl]hydrazone] 12

Yield 78%, red solid, mp 96°C - 98°C; MS m/z C₁₄H₁₁ClN₄O (286/288 M⁺, chlorine isotopes effect); HRMS (Calculated 286.0695, Found 286.0685). 1H NMR (400 MHz, DMSO-d₆): δ 7.66 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 2.27 (s, 3H, CH₃).

7) 5-Methylimidazo[1,2-a]pyridine-2,3-dione-3-[4-chlorophenyl]hydrazone] 13

Yield 30%, Yellow solid, mp 130°C - 132°C; MS m/z C₁₄H₁₁ClN₄O (286/288 M⁺, chlorine isotopes effect); HRMS (Calculated 286.0695, Found 286.0698). 1H NMR (300 MHz, DMSO-d₆): δ 7.43 (s, 1H, NH), 8.39 (d, J = 6.9 Hz, 1H), 7.64 (d, J = 6.9 Hz, 1H), 7.60 (d, J = 6.9 Hz, 2H), 6.88 (t, J = 6.9 Hz, 1H), 2.25 (s, 3H, CH₃).

2.1.2. General Procedures for Syntheses of Compounds 18, 19, 23, 24 and 29

Triethylamine (0.6 g, 0.006 mol) in THF (30 ml) and methanol (10 ml) was drop-wise added to a stirred solution of hydrazonoyl chloride and the appropriate azole (0.005 mol) at room temperature. Stirring was continued for 24 hours. The solvent was then removed and the solid precipitate was washed with water 50 ml and then washed with cold ethanol. The crude solid product was collected, dried and crystallized from hot ethanol.

1) Methyl 2-(3-amino-4H-1,2,4-triazol-4-yl)-2-(2-(4-chlorophenyl)hydrazono)acetate 18

Yield 50%, yellow solid, mp 255°C - 257°C; MS m/z C₁₂H₁₁C₁N₃O (294/295 M⁺, chlorine isotopes effect). 1H NMR (300 MHz, DMSO-d₆): δ 10.88 (s, 1H, NH), 7.95 (s, 1H, N=CHN, trizole ring), 7.35 (s, 4H, aromatic ring), 5.95 (s, 2H, NH₂), 3.74 (s, 3H, OCH₃). 13C NMR (100 MHz, DMSO-d₆): δ 203.0, 150.0, 149.0, 140.0, 136.0, 133.0, 131.0, 130.0, 127.0, 112.0, 111.0, 18.0.

2) 1-(3-amino-4H-1,2,4-triazol-4-yl)-1-(2-(2,5-dimethylphenyl)hydrazono)propan-2-one 19

Yield 40%, brown solid, mp 194°C - 196°C; MS m/z C₁₅H₁₄ClN₄O (296 M⁺, chlorine isotopes effect); HRMS (Calculated 296.0646, found 296.0647). 1H NMR (300 MHz, DMSO-d₆): δ 9.76 (s, 1H, NH), 7.89 (d, J = 8.0 Hz, 1H, C=O), 7.26 (s, 4H, aromatic ring), 7.15 (t, J = 7.7 Hz, 1H, aromatic ring), 7.07 (t, J = 7.6 Hz, 2H, aromatic ring), 2.47 (s, 3H, CH₃). 13C NMR (100 MHz, DMSO-d₆): δ 190.5 (C=O), 153.3 (N=CN, triazol ring), 142.28 (C, aromatic ring), 138.76 (CH, NN=CHN, trizol ring), 129.32 (C, aromatic ring), 126.42 (s), 117.45 (C, aromatic ring), 116.57 (CH, aromatic ring), 52.7 (OCH₃).

3) Methyl 2-(5-amino-1H-tetrazol-1-yl)-2-(2-(4-chlorophenyl)hydrazono)acetate 24

Yield 48%, pale yellow solid, mp 161°C - 162°C; IR (KBr): νmax cm⁻¹: 3214, 3168, 3111 and 1748. MS: m/z C₁₀H₁₀ClN₄O (296) [M+H]⁺. 1H NMR (300 MHz, DMSO-d₆): δ 10.24 (s, 1H, NH), 7.43 (d, J = 9.0 Hz, 2H, aromatic ring), 7.37 (d, J = 9.0 Hz, 2H, aromatic ring), 7.12 (s, 2H, NH₂), 3.79 (s, 3H, OCH₃). 13C NMR (100 MHz, DMSO-d₆): δ 106.88 (C=O), 156.5 (C=O), 141.9, 129.7, 127.3, 116.9, 116.5 (aromatic ring), 53.1 (OCH₃).

4) 1-(5-amino-1H-tetrazol-1-yl)-1-(2-(2,5-dimethylphenyl)hydrazono)propan-2-one 25

Yield 52%, yellow solid, mp 220°C - 222°C; IR (KBr): νmax cm⁻¹: 3300, 3000, 1660, 1540, 1450 and 1410. MS: m/z C₁₁H₁₀ClN₄O₂ (296) [M+H]⁺. HRMS (Calculated 296.0695, Found 296.0696). 1H NMR (300 MHz, DMSO-d₆): δ 9.80 (s, 1H), 8.04 (s, 1H), 7.73 (s, 1H), 7.70 (d, 2H), 7.59 (d, 2H), 3.86 (s, 3H), 2.27 (s, 3H, CH₃).
(s, 3H), 1.91 (s, 3H).

3. Results and Discussion

The reaction of picoline derivatives 3-6 with hydrazonyl chloride 1a in THF in the presence of Et$_3$N as a base at room temperature produced imidazo[1,2-a]pyridine 7-10 in 85% - 90% yield, while the reaction of hydrazonylchloride 1b with substituted picolines 3-6 under the same reaction conditions afforded the expected imidazo[1,2-a]pyridine-2-ones 11-13 in 30% - 70% yield (Scheme 1). The structure of the products was confirmed by the different spectroscopic analytical methods including IR, MS, $^1$HNMR and $^{13}$CNMR.

The reaction of 1 with 3-amino-1,2,4-triazole 14 in refluxing ethanol was reported by Shawali et al. to give imidazo[1,2-b]triazole 15 in very low yield [10]. On the other hand, and under the same reaction conditions, Graf reported that the reaction of 14 with hydrazonylchloride 1 (X = Ar) afforded the acyclic adducts 16 [11]. Treatment of 16 with refluxing AcOH/NaOAc led to formation of the cyclic fused product 18 via loss of a molecule of NH$_3$. The structure of 16 and 17 were determined by X-ray crystallography.

In this work, the reaction of hydrazonylchlorides 1b, c with 3-amino-1,2,4-triazole 14 in the presence of Et$_3$N and THF at room temperature (Scheme 2) afforded the acyclic adducts 18 and 19, respectively. This as-
Assignment is based on the appearance of the NH₂ group and the C=O group in both IR and NMR spectra. Similar to Graf product, the reaction is proposed to occur at the N4 of the triazole 14. The fused heterocyclic system reported by Shawali [10] was not obtained. Attempt to cyclize compounds 18 and 19 using AcOH/NaOAc (Graf method) was unsuccessful.

Graf reported [12] that the reaction of hydrazonylhalides 1 with 5-aminotetrazole 20 in refluxing ethanol produced compounds 22 via the rearrangement accompanied by loss of hydrazoic acid (HN₃) from the intermediate cycloaddition product 21. In this work; the reaction of hydrazonyl halides 1b, 1c with 5-aminotetrazole 20 in THF in the presence of Et₃N at room temperature afforded the acyclic adducts 23 and 24, respectively (Scheme 3).

The reaction of hydrazonylhalide 1a with 2-aminopyrimidine 25 was reported by Awadallah et al. [8] to produce the pyrimido[2,1-d]1,2,3,5-tetrazine 26. The reaction of 1b with 4, 6-dimethyl-2-aminopyrimidine 27 in THE in presence of Et₃N as a base at room temperature produced however, the acyclic adduct, 29. Two different possible isomeric structures are possible 28 and 29 (Scheme 4). The NMR data obtained provided an unambiguous confirmation that the actual obtained product is in fact compound 29 rather than compound 28. The assignment is based on the appearance of two CH₃ groups at the pyrimidine ring. In compound 28 these two CH₃ are identical as they are in the same chemical and electronic environment, so they should appear as one peak.
with an integration value corresponding to 6H. On the other hand, the two CH$_3$ groups in compound 29 are different and two peaks with equal integration are expected. $^1$HNMR spectra obtained supported structure 29 rather than 28. The mass spectra form compound 29 in both positive mode 234 [M+1]$^+$ and negative mode 232 [M-1]$^-$ is shown in Figure 1.

4. Conclusion

A new series of heterocyclic compounds was synthesized via the reaction of Nitrilimines with 2-aminopicoline, 3-amino-1,2,4-triazole, 5-aminotetrazole and 2-aminopyrimidine. The structures of the products were characterized by IR, $^1$H-NMR, $^{13}$C-NMR and MS. The melting points of the synthesized compounds are listed in Table 1.

![Mass spectra for compound 29 in both positive and negative mode.](image)

**Table 1.** The melting points of the synthesized compounds.

<table>
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<tr>
<th>Comp.</th>
<th>M.F.</th>
<th>M.W</th>
<th>M.P$^\circ$C</th>
<th>Comp.</th>
<th>M.F.</th>
<th>M.W</th>
<th>M.P$^\circ$C</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>C$<em>{15}$H$</em>{13}$ClN$_4$</td>
<td>284</td>
<td>152 - 155</td>
<td>13</td>
<td>C$<em>{15}$H$</em>{12}$ClN$_4$O</td>
<td>286</td>
<td>232 - 235</td>
</tr>
<tr>
<td>8</td>
<td>C$<em>{15}$H$</em>{13}$ClN$_4$</td>
<td>284</td>
<td>174 - 177</td>
<td>18</td>
<td>C$<em>{15}$H$</em>{13}$ClN$_4$O</td>
<td>284</td>
<td>255 - 257</td>
</tr>
<tr>
<td>9</td>
<td>C$<em>{10}$H$</em>{11}$ClN$_4$O</td>
<td>286</td>
<td>96 - 98</td>
<td>23</td>
<td>C$<em>{12}$H$</em>{17}$N$_7$O</td>
<td>273</td>
<td>161 - 162</td>
</tr>
<tr>
<td>10</td>
<td>C$<em>{14}$H$</em>{12}$ClN$_5$O</td>
<td>333</td>
<td>130 - 132</td>
<td>24</td>
<td>C$<em>{13}$H$</em>{16}$N$_6$O</td>
<td>295</td>
<td>180 - 182</td>
</tr>
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References

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